Outcomes of Men who Present with Elevated Serum PSA (>20 ng/mL) to an Inner-City Hospital

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Introduction: We report the incidence, clinicopathologic features, and outcomes of men who presented to an inner-city hospital with serum PSA >20 ng/ml.

Materials and Methods: Five-hundred-sixty men underwent a transrectal ultrasound needle-guided biopsy of the prostate for elevated PSA >4 ng/ml with or without an abnormal digital rectal examination.

Results: Of the 560 men, 65 (12%) were found to have a serum PSA >20 ng/ml, and 57 (10%) were diagnosed with prostate cancer. In the group of 57 men with cancer, the positive predictive value of PSA alone was 72% for PSA levels of 20–29.99 ng/ml and 100% for PSA >30 ng/ml. Of the 57 men, 18 underwent definitive therapy, 24 underwent androgen deprivation, 8 refused treatment or were lost to follow-up, and 7 were treated on protocol. An additional seven men with cancer refused therapy or were lost to follow-up, thus giving a total of 15 (26%) men who were noncompliant to medical advice.

Conclusions: Serum PSA >30 ng/ml is an almost certain predictor of the presence of prostate cancer. Aggressive prostate cancer education and screening programs are needed in our inner cities in order to detect prostate cancer at an earlier, treatable stage.

Key words: prostate-specific antigen ■ prostate ■ cancer ■ androgen deprivation

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Since the mid-1990s, prostate cancer mortality rates have continued to decline,[1,2] even though prostate cancer remains the second most common cause of cancer-related death in American men aged >45 years.[3] Previously, we reported that inner-city African-American men were four times more likely to present with advanced prostate cancer.[4] Death from prostate cancer is usually caused by the continued growth of the advanced disease in the face of androgen deprivation therapy (ADT).

Studies have clearly demonstrated that annual prostate cancer screening can lead to a stage migration[5] and prostate-specific antigen (PSA) migration (i.e., men with prostate cancer are presenting with lower PSA levels and thus lower-stage disease),[6] and both translate into improved biochemical survival. But what of the men who present to their treating urologists with extremely elevated serum PSA levels? What are their chances of harboring cancer? Heyns et al. reported that a PSA level >50 ng/ml was associated with a 96% positive predictive value for prostate cancer.[7] Gerstenbluth et al. recommended that some highly select patients did not need a prostate biopsy before ADT because the positive predictive value of serum PSA levels >50 ng/ml in detecting cancer is 98.5%.[8] In addition, the morbidity from prostate biopsy is minimal, reported at <1%.[9] With the low risk of complications and high yield from elevated serum PSA (≥50 ng/ml), we believe that highly select symptomatic men with extremely high serum PSA could be started on immediate ADT even without a tissue diagnosis of prostate cancer. Herein, we present a contemporary series composed of 65 inner-city men presenting to a tertiary-care hospital with unusually elevated serum PSA (≥20 ng/ml). In this cohort, we report the incidence and clinicopathologic features of prostate cancer in this group, as well as treatment outcomes.

METHODS

Study Population

Between January 2003 and May 2006, 560 consecutive men underwent a transrectal ultrasound needle-guided biopsy of the prostate at Shands Jacksonville for an abnormal digital rectal examination or an elevated serum PSA (>4.0 ng/ml) or both. Of the 560 men, 65 presented with serum PSA levels >20 ng/ml and were included in the study. Institutional review board approval was obtained to query medical records for pertinent

clinical information.

Pretreatment evaluations included medical history; physical examination, including digital rectal examination; and measurement of free and total PSA levels (Abbott Laboratories, Abbott Park, IL).

Transrectal Ultrasonography and Prostate Biopsy

A 7.5-MHz transrectal probe (B-K Medical Systems Inc., Wilmington, MA) was introduced into the rectum. Transverse and sagittal images were obtained. Three-dimensional volume was calculated by multiplying the prostate gland's height (cm) by width (cm) by depth (cm) and dividing by 0.51.[10] Prostate-specific antigen density (PSAD) was calculated by dividing serum PSA level by prostate weight (g); a PSAD >0.2 ng/ml/g is considered normal.[10] Specific ultrasonographic findings are not characterized because each patient underwent an extended biopsy (≥10 cores) regardless of the ultrasonographic appearance of the prostate. Biopsies were obtained transrectally by utilizing an 18-gauge spring-loaded biopsy gun.

Tumor Grading and Staging

Biopsy specimens were graded histologically according to the Gleason grading system.[11] The 2002 tumor-node-metastasis (TNM) staging system was used for clinical staging.[12] Bone scans or computed tomography scans of the pelvis or both were obtained according to the preference of the treating urologist.

Treatment and Outcome Assessment

Clinic and hospital records were reviewed for several key factors, including prostate cancer incidence, tumor stage, tumor grade, treatment, outcome, development of androgen-insensitive disease and death. Failure after prostatectomy was defined as any detectable PSA. Failure after cryosurgery was defined as a persistently rising PSA profile with or without a biopsy-confirmed diagnosis. The ASTRO criterion—three consecutive rises in PSA—was used to define failure after radiation therapy.[13] The development of androgen-insensitive disease was defined as a rising PSA profile in the presence of a castrated state (testosterone <50 ng/ml).

Table 1. Demographics and clinicopathologic features of 65 men with serum PSA levels ≥20 ng/ml

	All	Negative Initial Biopsy	Curative Intent	Androgen Deprivation	No Treatment	Protocol
Total No.	65	7*	18	24	8	7
Median Age (Range)	67 (52–88)	73 (52-81)	64 (52-80)	70.5 (56-88)	61 (52–81)	63 (58–81)
Race						
Caucasians	23	2	8	8	1	3
African Americans	41	5	10	15	7	4
Others	1	--	--	1	--	--
Insurance Status						
Commercial	13	1	9	13	6	4
Governmental	50	7	9	9	3	2
None	2	--	--	2	--	--
Median PSA (Range)	49.2 (20.3–5000)	22.5 (20.3–93.7)	26.7 (20.46–125.1)	98.5 (20.36-5,000)	97.8 (20.94-4418)	1,125.5 (143–2,746)
Median Free PSA (Range)	4.3 (0.9–289.3)	N/A	1.42 (0.9-7.36)	8.5 (1.6–47.11)	70.3 (7.3-17.4)	153 (16.7–289.3)
Median Free/Total % (Range)	6.8 (2.7–22.1)	N/A	6.1 (2.7-9.9)	6.5 (4.1–22.1)	24 .7 (7.3–17.4)	23 (10.3–12.7)
Clinical Stage						
Organ confined	27	--	18	7	4	2
Locally Advanced	10	--	--	4	1	1
Metastatic	20	--	--	13	3	4
Median Gleason Score	8 (6–10)	--	8 (7–10)	8 (6–10)	9 (6–9)	9 (8–9)
Median Follow-Up (Months)	7.5 (0–33)	5.0 (0–24)	7.5 (0–30)	13.5 (3–33)	3 (0–9)	10.5 (0–21)

* One patient found to have cancer (PSA <20 ng/mL) on follow-up biopsy and thus was not included in evaluation; N/A: not assessed (not enough data points)

Data Analysis

The association between a covariate and a dichotomous outcome variable—such as occurrence of prostate cancer, rising PSA profile and death from prostate cancer—was evaluated by the Wilcoxon rank sum test. Covariates under consideration were age, height, weight, race, clinical stage, initial PSA, free PSA, free/total (F/T) % PSA and prostate volume. Because of the limited sample size, the multivariate analysis was not performed. Note that the number of patients without prostate cancer was only seven, and the number of deaths from prostate cancer was only 12, so the results should be considered as tentative.

Fisher's exact tests were also performed. Because the results from the Wilcoxon rank sum tests and the Fisher's exact tests were similar, all reported p values were obtained by two-sided Wilcoxon rank sum test.

RESULTS

Our records demonstrated that of the 560 consecutive men undergoing transrectal ultrasound-guided prostate biopsies, 65 (12%) presented with serum PSA values ≥20 ng/ml. Of the 65 men, 57 (88%) were found to have cancer. Table 1 describes the demographic and clinicopathologic findings of the entire study cohort. Of the eight men without cancer, one underwent repeat prostate biopsy and was found to have cancer. This patient's initial biopsy demonstrated atypia. Subsequent serum PSA before repeat biopsy was <20 ng/ml and thus the man was not included in the present analysis. Of the remaining seven men whose prostate biopsies did not demonstrate cancer, one underwent repeat biopsy and still did not demonstrate cancer, one refused a repeat biopsy, and five were lost to follow-up. Median follow-up for the entire cohort was nine months (range 0–33 months).

The positive predictive value of various PSA levels ≥20 ng/ml alone or in combination with an abnormal digital rectal examination are listed in Table 2. The positive predictive value of PSA alone in this setting was 72% for PSA levels of 20–29.99 ng/ml and 100% for PSA levels ≥30 ng/ml. With the addition of an abnormal digital rectal examination, the positive predictive values for these PSA ranges increased to 90% and 100%, respectively. Higher PSA levels (>30 ng/mL) were significantly associated with the occurrence of prostate cancer (p=0.007).

Of the 57 patients with cancer, 18 (32%) were treated with curative intent: radical prostatectomy (RP) alone (n=4), cryosurgical ablation alone (n=2), and external beam radiotherapy with ADT for ≥2 years (n=12). One of the four men who underwent RP had positive surgical margins, and all four had Gleason scores of 8 on final pathologic evaluation. The patient with the positive surgical margins and one other man developed PSA recurrence nine and 21 months after surgery, respectively. No recurrence was evident in the cryosurgical ablation group. Only one patient in the group treated with external beam radiation and ADT failed, based on ASTRO criteria. Three of the 18 men treated with curative intent died from causes unrelated to prostate cancer or prostate cancer treatment.

Of the 57 men with cancer, 24 (42%) were treated with castration: surgical (2, 8%) and medical (22, 92%). Only one of the men treated with medical castration had failed previous definitive therapy, radiation therapy. Medical castration was performed by administering luteinizing hormone-releasing hormone (LHRH) agonist: leuprolide acetate injectable alone (9, 37.5%), leuprolide acetate implant alone (3, 12.5%) or goserelin injectable alone (7, 29%). Another three (12.5%) men treated with castration had been treated initially with one of the agents listed above in combination with an antiandro-

Table 2. Predicting the histological diagnosis of prostate cancer using PSA ranges alone or in combination with digital rectal examination findings

PSA Range (ng/mL)	# Points	# with Ca on Biopsy	% Positive Predictive Value
PSA Alone			
20–29.9	25	18	72%
≥30	39	39	100%
Totals	64	57	89%
PSA with Normal DRE			
20–29.9	15	9	60%
≥30	5	5	100%
Total	20	14	70%
PSA with Abnormal DRE			
20-29.9	10	9	90%
≥30	34	34	100%
Total	44	43	98%

* One patient found to have cancer (PSA <20 ng/mL) on follow-up biopsy and thus was not included in evaluation; N/A: not assessed (not enough data points); DRE: digital rectal examination

gen, in an effort to prevent an exacerbation of present symptoms, followed by LHRH agonist treatment alone. Thirteen (54%) of the 24 men developed a rising PSA profile while castrated. It was found that higher initial PSA level was significantly associated with an increase in serum PSA while on ADT (p=0.03). Four men refused treatment after the initiation of ADT. In this cohort, nine of the 23 men died (seven of metastatic prostate cancer and two of causes unrelated to prostate cancer or prostate cancer treatment).

Eight (14%) of the 57 men with cancer refused the initial recommendation of ADT. Subsequently, one started therapy and five died of their disease. Two (4%) of the 57 patients were lost to follow-up. Another seven men (12%) were treated on one of two clinical protocols. Only one of these men was lost to follow-up and two developed a rising PSA profile. No deaths were reported in this cohort.

Overall, 15 (26%) of 57 patients refused therapy or were lost to follow-up. Seventeen (30%) of the 57 men died during this study, 12 as a result of their disease. It was found by univariate analysis that worse clinical stages and higher initial PSA levels were significantly associated with death from prostate cancer (p=0.004 and 0.016, respectively).

DISCUSSION

The concentration of serum PSA in untreated patients with prostate cancer is proportional to the volume of cancerous tumor as well as to the clinical stage.[14] Our analysis confirms Gerstenbluth and colleagues' results that, alone, serum PSA level ≥20 ng/ml had a positive predictive value of 87% (72% in our series) When the PSA level was increased to >50 ng/ml, they reported a positive predictive value of 98.5% accuracy in predicting the presence of prostate cancer on tissue biopsy[8] (approximately 100% in our series when PSA was >30 ng/ml). These results are in line with results reported by Heyns and coworkers.[7] Furthermore, the addition of an abnormal digital rectal examination increased our positive predictive value of serum PSA ≥20 ng/ml to 98%, which is similar to predictive values previously reported in the literature.[8] Gerstenbluth et al. conclude that in highly select men with extremely elevated serum PSA, one could forgo initially biopsy and immediately proceed to treatment.[8] With the high yield from elevated serum PSA (≥50 ng/ml), we believe that highly select men with extremely high serum PSA and symptomatic disease could be started on immediate ADT even without a tissue diagnosis of prostate cancer.

In addition to the strong positive predictive value of detecting prostate cancer in a man with an extremely elevated serum PSA, we were able to demonstrate three other important factors in this cohort that have never been reported before in the literature. These factors included a high noncompliance rate for ADT, a rapid time to androgen-insensitive disease, and an overall high death rate. Surprisingly, these factors were elicited with limited follow-up. Median follow-up of this study was 7.5 months. It then stands to reason that, with adequate follow-up, an even higher rate of noncompliance, development in androgen-insensitive disease and overall death rate may emerge.

When questioned in depth about their noncompliance, men treated with ADT reported a high incidence of debilitating side effects (e.g., hot flashes, weight change, breast tenderness) in addition to feelings of demasculinization. Side effects from ADT are well documented.[15] These side effects should be conveyed to the patients before the initiation of ADT and monitored on subsequent visits. In addition, the men should be told that various agents are available to ameliorate these side effects.[16] Proper counseling and monitoring and treatment of side effects may decrease the incidence of noncompliant behavior.

Another interesting finding in the present study was the rapid development of androgen-insensitive disease. Previously it has been demonstrated that ADT can continue for an average of 33 months before documented tumor growth (e.g., rising PSA profile).[17] The median time to the development of androgen-insensitive disease in our study was <15 months. Data were not available depicting the pretherapy PSA doubling time, but it stands to reason that a more aggressive disease may have a shorter PSA doubling time. Other centers should assess this concept to determine whether pre-ADT PSA doubling time is associated with disease progression.

Finally, the most compelling data point presented in the present study is an overall death rate of 30%. Fully 70% of these deaths were due to prostate cancer. With longer follow-up, one could expect to see an even higher overall mortality rate. Two key components stand out in this particular setting. First, as in other settings of advanced prostate cancer, early ADT may prove beneficial in men with advanced prostate cancer.[18] Because of the high mortality rate of this cohort, men found to have prostate cancer with an initial serum PSA >30 ng/ml should not only be offered immediate ADT but should also be considered for early combinational therapy (i.e., ADT with chemotherapy) or an investigational protocol.

Our study has several limitations. First, this was a small retrospective study from a single institute. Not only could biases have been introduced in patient selection and treatment but also this group might not represent other men presenting with extremely high PSA in the face of prostate cancer. Furthermore, longer follow-up is needed to better determine compliance, development of androgen-insensitive disease, and overall survival. Finally, PSA doubling time has previously been linked to prostate cancer survival.[19] It would have been extremely useful if we could have known the PSA doubling time before and after therapy in order to evaluate

its prognostics significance in this setting.

Each patient should be evaluated on individually, and diagnostic and treatment modalities should be recommended based on the patient's clinic history and physical. If a diagnosis of cancer is suspected and treatment is contemplated, a prostate biopsy can be performed if medically indicated. Our threshold for biopsying and recommending treatment in a younger man (i.e., <65 years) with these disease characteristics is quite low because, in this cohort, we see that advanced prostate cancer can adversely affect overall survival.

Inner-city facilities must continue to strive to find ways to decrease the incidence of men presenting with advanced prostate cancer. To accomplish this, we must target inner-city men and provide prostate cancer educational seminars, as well as prostate cancer screening clinics. With aggressive prostate cancer screenings, we would expect to see a stage migration toward organ-confined disease, which is readily treatable with our current modalities.

In conclusion, serum PSA>30 ng/ml, combined with an abnormal digital rectal examination, is 100% accurate in predicting the presence of prostate cancer with tissue biopsy. If surgery or radiation therapy is considered for presumably localized or locally advanced disease, biopsy is warranted. The majority of inner-city men presenting with extremely elevated serum PSA and prostate cancer were treated with ADT. For unknown reasons, nearly a third of patients were noncompliant with physician recommendations for ADT. In patients treated with ADT who were compliant, nearly 40% developed androgen-insensitive disease, and overall a third of the men died during our short follow-up. Aggressive prostate cancer education and screening programs are needed in our inner cities in an effort to detect prostate cancer at an earlier, more treatable stage.

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